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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,672	EATON ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,11-14 and 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,11-14 and 17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0705*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/01/2005 has been entered.

Claims 4–6, 11–14 and 17–26 are pending and being examined.

Maintained Formal Matters, Objections And/Or Rejections:

Claim Rejections - 35 USC § 112

Claims 4–6, 12–14 and 17–26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that they have conveyed with reasonable clarity to those skilled in the art that Applicants were in possession of the claimed invention. Applicants argue that SEQ ID NO: 9 inherently discloses the claimed invention. Applicants argue that the Office misstates the test for compliance with the written description requirement. Applicants' arguments have been fully considered but they are not persuasive. Paragraph 0196 discloses that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides. There is no evidence of record that this generic disclosure would reasonably lead

the skilled artisan to the particular species of starting amino acid that is amino acid #34. This generic disclosure does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the claimed invention. This generic disclosure does not describe amino acid #34 as the starting amino acid residue for the PRO874 polypeptide.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4–6, 11–14 and 17–26 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to or encompass an isolated nucleic acid molecule comprising the PRO874 polynucleotide (SEQ ID NO: 9), an isolated nucleic acid molecule having a recited % identity to the PRO874 polynucleotide, an isolated nucleic acid molecule that hybridizes to the PRO874 polynucleotide, a vector comprising the isolated nucleic acid molecule and a host cell comprising the vector.

The present application characterizes the PRO874 polypeptide and polynucleotide as follows:

> [0036] FIG. 9 shows a nucleotide sequence (SEQ ID NO: 9) of a native sequence PRO874 cDNA, wherein SEQ ID NO: 9 is a clone designated herein as "DNA40621-1440".
>
> [0037] FIG. 10 shows the amino acid sequence (SEQ ID NO: 10) derived from the coding sequence of SEQ ID NO: 9 shown in FIG. 9. Page 11.

DNA40621-1440 is more highly expressed in normal lung than as compared to lung tumor. Example 18, Page 141.

Figure 10 also provides various structural features of the PRO874 polypeptide, presumably based on homology with domains of other known proteins. However, one skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during evolution. See Henikoff (Science. 1997 Oct 24;278(5338):609-14), page 609, Abstract. Accordingly, one skilled in the art would not accept mere homology as establishing a function of protein because gene products may acquire new specificities, altered recognition properties, or modified functions. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role. Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein cannot be automated. However, homology can be used to guide further research. See Henikoff, paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2.

The PRO874 polynucleotide appears to encode a secreted protein/membrane-bound protein/receptor. The present specification discloses that secreted proteins and membrane-bound proteins and receptors have widely varying activities (paragraphs 0002-0004). This finding establishes that secreted proteins and membrane-bound proteins and receptors have very diverse functions and makes it clear that classification of a protein as a secreted protein or a membrane-bound protein or receptor does not identify it as having a specific function. The specification provides no basis for concluding which, if any, of the varied activities of secreted proteins and membrane-bound proteins and receptors is possessed by the PRO874 polypeptide. The examiner is aware that the present claims are drawn to a polynucleotide. However, there is no evidence that a skilled artisan would have appreciated the identification of the PRO874 polynucleotide as encoding a secreted protein/membrane-bound protein/receptor, without more, would have suggested any specific patentable utility.

The disclosed uses for PRO polynucleotides and polypeptides in general (paragraphs 0316-0360) are not specific to the PRO874 polynucleotide.

Example 18 discloses that DNA40621-1440 is more highly expressed in normal lung as compared to lung tumor. However, the specification provides no information regarding the absolute values of the differences in transcript levels. The literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (page 408, middle of right column). Hu states:

"It is not uncommon to see expression changes in micro-array experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. When comparing expression levels of disease to normal tissue, one expects an enrichment of known disease-related genes to appear in the altered expression group. MedGene provided a unique opportunity to test this notion in the context of existing knowledge on a novel breast cancer micro-array dataset. For genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. This reflects the many genes whose role in breast cancer may not involve large changes in expression in sporadic tumors (e.g., BRCA1 and BRCA2) and genes whose modest changes in expression may be unrelated to the disease. Strikingly, among genes with a 10-fold change or more in expression level, there was a strong and significant correlation between expression level and a published role in the disease, providing the first global validation of the micro-array approach to identifying disease-specific genes." Paragraph bridging pages 411-412.

"The results derived from MedGene have two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level changes. Second, any genes with 10-fold changes or more are likely to be related to breast cancer and warrant attention. It is likely that this threshold will change depending on the disease as well as the experiment." Page 412, left column, full paragraph 1.

"Interestingly, the observed correlation was only found among ER-positive tumors, not ER-negative. This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently. The MedGene approach identified a set of relatively understudied, yet highly expressed genes in ER-negative tumors that are worthy of further examination (Table 3)." Page 412, left column, full paragraph 2.

Although Hu indicates that the observed correlation was only found among ER-positive tumors, not ER-negative, Hu's approach identified a set of relatively understudied, yet highly expressed genes in ER-negative tumors that are worthy of further examination. This is consistent with Hu's conclusion that even when expression changes as small as 2-fold are statistically significant, it is not always clear if they are biologically meaningful. These small changes in expression may reflect genes whose role in cancer may not involve large changes in expression or genes whose modest changes in expression may be unrelated to the disease.

The examiner understands Hu's use of the term "biologically relevant," "biologically meaningful," or "relevant to the study" to include diagnostic relevance, which is supported by LaBaer (Nat Biotechnol. 2003 Sep;21(9):976-7), which teaches:

> In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. Page 976, paragraph bridging middle and right columns.

A gene whose change in expression is attributable to disease-independent differences between the samples cannot be used as a diagnostic indicator of the disease.

The utility of the claimed polynucleotides lies in their ability to differentiate normal lung from lung tumor. The specification discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0530.

It is unknown what level of difference is being reported or how many samples were tested. The first Grimaldi declaration (EXHIBIT 1, 12/10/2004) indicates that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. In practicing the invention some value for PRO874 polynucleotide expression must be obtained in order to distinguish normal tissue from tumor tissue. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool,

which Applicants have not provided. Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue.

In addition, Wang (Trends Pharmacol Sci. 1996 Aug;17(8):276-9) indicates that differential display is the first of many steps required in the discovery of a novel pharmacological target, especially given that the function of the factor is most likely unknown. Therefore, further action should be taken to characterize the functions of a particular gene of interest, including ... validation for the importance of the gene in disease processes. See page 279, column 2, full paragraph 1.

The claims are drawn to a vector comprising the claimed nucleic acid molecules and a host cell comprising the claimed vector. The specification discloses:

> Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production .... Page 79, paragraph 0292.

A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility or a method of making a material that itself has no specific, substantial and credible utility are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define substantial utilities. It is therefore appropriate to consider the utility of the encoded

polypeptide in relation to the claimed vectors and host cells. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. Applicants' reliance on a general correlation between changes in the level of mRNA and a corresponding change in the level of the encoded protein is wholly consistent with the examiner's finding that the skilled artisan would not know if or how expression of the PRO874 polypeptide would change in tumors, which is wholly consistent with contemporary knowledge in the art. Even if one were to assume that the disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression the skilled artisan still would not know if the assumed change in PRO874 polypeptide expression is tumor-dependent or tumor-independent because it is unknown if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent. It is clear that Applicants seek a per se rule, that any disclosed difference in mRNA expression is significant, reliable, relevant, and tumor-dependent and that any such difference would require a per se rule of utility for the encoded polypeptide and antibodies thereto. This standard, however, is not what the art teaches. For example, Haynes (Electrophoresis. 1998 Aug;19(11):1862-71) discloses that:

> "Interpretation of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression" (page 1863, left column, full paragraph 1),

Haynes goes on to state:

> "These results suggest that even for a population of genes predicted to be relatively homogenous ..., the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (page 1863, left column, full paragraph 1).

Haynes further teaches:

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column, full paragraph 2).

Because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis the skilled artisan would not know if the disclosed change in PRO874 mRNA transcripts is associated with a corresponding change in the level of PRO874 protein. Hence, the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer.

This conclusion is supported by Hancock (J Proteome Res. 2004 Jul-Aug;3(4):685):

> "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" (full paragraph 2);

Allman (Blood. 1996 Jun 15;87(12):5257-68):

> "germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations" (page 5257, paragraph bridging left and right columns);

the Polakis declaration (EXHIBIT 3, 12/10/2004):

> "... there have been published reports of genes for which such a correlation does not exist, ..." (paragraph 6).

Molecular Biology of the Cell, 3rd ed. (EXHIBIT 1, 07/01/2005):
"other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 453, last full paragraph);

Molecular Biology of the Cell, 4th ed. (EXHIBIT 4, 12/10/2004 AND EXHIBIT 2, 07/01/2005):
"the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps [from DNA to protein] is performed" (page 363, last full paragraph and page 364, Figure 6-90); and

Lewin (EXHIBIT 3, 07/01/2005):
"production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848).

Meric (EXHIBIT 5, 07/01/2005) also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA.

Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in *Brenner v. Manson*:

> But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the PRO874 polypeptide would change in tumors. The specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Therefore, the disclosure that DNA40621-1440 is more highly expressed in normal lung as compared to lung tumor does not impute a specific and substantial utility to the PRO874 polynucleotide. Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Thus, the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polynucleotides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 4–6, 11–14 and 17–26 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicants argue that example 18 and the first Grimaldi declaration (EXHIBIT 1, 12/10/2004) establish that the PRO874 gene is differentially expressed in lung tumors cancers and that the PRO874 gene, polypeptide and antibodies thereto are useful as diagnostic tools. Applicants' arguments have been fully considered but they are not persuasive. The assertions that "Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "The precise levels of gene expression are irrelevant" (paragraph 7), and "If a difference is detected, ... the gene and its corresponding polypeptide ... are useful for diagnostic purposes" (paragraph 7) are conclusory and unsupported. Furthermore, the declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor and normal tissue. The specification does not teach the level of reproducibility or reliability of the results seen in Example 18. There are no absolute levels of PRO874 mRNA in control or tumor tissue disclosed. The likelihood that the level of PRO874 from a tissue sample from a patient with cancer would be higher or lower when compared with normal tissue is unknown. It is unknown how many samples would be needed or what sensitivity would be needed. It is unknown if the normal tissue would have to be a pooled sample or from a single individual. Applicants only teach that PRO874 mRNA was "more highly expressed in" normal lung as compared to lung tumor, and this does not enable the skilled

artisan to differentiate between expression levels in order to diagnose any diseases. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan and significant further experimentation is necessary.

The utility of the claimed polynucleotides lies in their ability to differentiate normal lung from lung tumor. The specification discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0530.

It is unknown what level of difference is being reported or how many samples were tested. The first Grimaldi declaration (EXHIBIT 1, 12/10/2004) indicates that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. In practicing the invention some value for PRO874 polynucleotide expression must be obtained in order to distinguish normal tissue from tumor tissue. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool, which Applicants have not provided. Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to

distinguish normal tissue from tumor tissue. Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant.

Applicants argue that the Office mischaracterizes Applicants position. Applicant's arguments have been fully considered but they are not persuasive. The Grimaldi declaration (EXHIBIT 2, 12/10/2004) asserts that:

> "Comparison of gene expression levels in normal versus diseased tissue has important implications both diagnostically and therapeutically." Paragraph 6.
>
> "... identification of both gene expression and protein expression enables more accurate tumor classification ..." Paragraph 7.

The Ashkenazi declaration (EXHIBIT 5, 12/10/2004) asserts that:

> the "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment." Paragraph 6.

Applicants are arguing that whatever the expression level and whatever the correlation, the claimed polynucleotides and the polypeptides they encode are useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Furthermore, the specification does not provide any information regarding more accurate tumor classification.

Applicants argue that the pending claims are not defined by the polypeptide sequence they encode. Applicants' arguments have been fully considered but they are not persuasive. The examiner has been and is aware that the present claims are drawn to polynucleotides. However, a claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility or a method of making a material that itself has no specific, substantial and credible utility are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define substantial utilities. The claims are drawn to a vector comprising the claimed nucleic acid molecules and host cells comprising the claimed vector. The specification discloses:

> Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production .... Page 79, paragraph 0292.

It is therefore appropriate to consider the utility of the encoded polypeptide in relation to the claimed vectors and host cells.

Applicants argue that the standard for establishing a use is not absolute certainty, and thus a necessary correlation between mRNA levels and protein levels is not required. Applicant's arguments have been fully considered but they are not persuasive. Applicants have asserted that polynucleotides whose expression is has been shown to be increased or decreased in tumors compared to the corresponding normal tissue are useful as diagnostic tools for cancer. See page 12 of the response filed 07/01/2005. Applicants also assert that it is well-established in the art that in general, the level of protein is positively correlated to the level of mRNA. See page 14 of the response files 07/01/2005. If one is to accept Applicants' assertions then there must be a necessary positive correlation between PRO874 mRNA expression and PRO874

polypeptide expression in order for the specification to enable use of the PRO874 polypeptide and antibodies thereto as the asserted cancer diagnostic or therapeutic. Applicants have not provided any testing of the role, activity, or expression of the PRO874 polypeptide.

Applicants argue that Allman supports Applicants' position because Allman's results were unanticipated. Applicant's arguments have been fully considered but they are not persuasive. If one is to argue, as Applicants have argued, that because PRO874 transcripts are differentially expressed in tumors it is more likely than not that the PRO874 polypeptide is differentially expressed in tumors, and therefore the PRO874 polypeptide and antibodies can be used for tumor diagnosis, then one must also accept the argument that because resting B cells and germinal center B cells express similar BCL-6 mRNA levels it is more likely than not that the BCL-6 protein is not differentially expressed in these two cell populations, and therefore the BCL-6 protein and antibodies thereto cannot be used as a marker for germinal center B cells. One must also accept the argument that because germinal center B-cells express dramatically more BCL-6 protein than resting B cells it is more likely than not that BCL-6 mRNA is differentially expressed in these two cell populations, and therefore BCL-6 mRNA can be used as a marker for germinal center B-cells. Allman indicates that this is not so and therefore Allman does not support Applicants' position. The fact that it was unexpected that increases in BCL-6 protein were not correlated with a corresponding change in the level of BCL-6 mRNA only establishes that the skilled artisan would not know if or how PRO874 polypeptide expression changes in tumors. To argue that Allman supports applicants' position because Allman did not obtain the anticipated results is akin to arguing that the skilled artisan could experiment with PRO874 mRNA and polypeptide levels and determine for themselves how to use the claimed

invention. Applicants have not provided any testing of the role, activity, or expression of the PRO874 polypeptide.

In support of the assertion that changes in mRNA are positively correlated with changes in protein levels Applicants refer to the second Grimaldi declaration (EXHIBIT 2, 12/10/2004), the Polakis declaration (EXHIBIT 3, 12/10/2004). Applicants argue that the statements of Grimaldi and Polakis are supported by Molecular Biology of the Cell, 3rd ed. (EXHIBIT 1, 07/01/2005) and Molecular Biology of the Cell, 4th ed. (EXHIBIT 4, 12/10/2004 AND EXHIBIT 2, 07/01/2005). Applicants argue that additional support is found in Zhigang (EXHIBIT 4, 07/01/2005) and Meric (EXHIBIT 5, 07/01/2005).

The Grimaldi declaration (Exhibit 2, 12/10/2004) has been considered. However, the facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a change in PRO874 polypeptides levels in tumors as compared to their normal tissue counterparts. In the present case it is unknown if the reported differences in PRO874 mRNA expression are tumor-dependent or tumor-independent. The declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by Hancock (J Proteome Res. 2004 Jul-Aug;3(4):685) and the declaration of

Dr. Polakis under 37 CFR 1.132 (Exhibit 3, 12/10/2004). The assertion that PRO874 polypeptide expression is useful regardless of the correlation between PRO874 mRNA expression and PRO874 polypeptide expression because it would allow more accurate tumor classification is akin to asserting that whatever the expression level and whatever the correlation, the PRO874 polypeptide and antibodies are useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect, characterize or classify the tumor. Such an asserted utility is not specific to the PRO874 gene or polypeptide and is analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

The Polakis declaration (Exhibit 3, 12/10/2004) has been considered. However, the facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a change in PRO874 polypeptides levels in tumors as compared to their normal tissue counterparts. The declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. There is no evidence of record that either the

PRO874 polynucleotide or the PRO874 polypeptide were abundantly expressed. The specification does not teach the level of reproducibility or reliability of the results seen in Example 18. Given the paucity of information regarding PRO874 expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO874 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO874 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. Even if the examiner were to assume that the disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO874 transcripts is disease-dependent or disease-independent. While Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to Dr. Polakis. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis.

Applicants argue that the examiner does not address the teachings of Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 07/01/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 2, 07/01/2005) and Lewin (Exhibit 3, 07/01/2005). Applicant's arguments have been fully considered but they are not persuasive. None of this evidence provides any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Consideration of the totality of the evidence provided leads to the conclusion that a skilled artisan would not know if or how PRO874 polypeptide expression would change in tumors.

It is acknowledged that Zhigang (Exhibit 4, 07/01/2005) presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1), and unlike Zhigang, Applicants have not provided any testing of PRO874 polypeptide expression. The application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Further experimentation would be required in order to identify or reasonably confirm a "real world" context of use.

It is acknowledged that Meric (Exhibit 5, 07/01/2005) states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells" (page 971, right column, first paragraph of "Introduction"). However, the specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO874 polypeptide. Therefore, the difference, if any, in PRO874 polypeptide expression between cancer cells and normal cells is unknown, and

thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner is not arguing that the techniques that measure gene levels, such as microarray analysis, differential display, and quantitative PCR, are without merit. The examiner is arguing that Applicants have failed to establish the correlation between a change in PRO874 mRNA expression and a change, if any, in PRO874 polypeptide expression. The examiner is not requiring that a change in the level of a particular mRNA must always be correlated with a corresponding change in the level of the encoded protein. The examiner is not arguing that there is no positive correlation between a change in the level of a particular mRNA with a change in the level of the encoded protein. The examiner is arguing that the change in PRO874 transcripts must be tumor-dependent and there must be a corresponding change in the level of the PRO874 polypeptide in order for the skilled artisan to use the PRO874 polynucleotide and polypeptide as the asserted diagnostic. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumors. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein without any evidence of the expression of the PRO874 polypeptide in normal tissue or tumor

tissue. The inherent lack of certainty in this general correlation results in a failure to prove practical utility for the PRO874 polypeptide and antibodies.

Conclusion

No claims are allowable.

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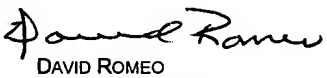

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APRIL 3, 2006